

Contemporary Drug Synthesis

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Preface

Armed with a vast amount of knowledge acquired at school, along with a degree in chemistry, you are starting your career in the pharmaceutical industry. You may be working in medicinal chemistry, process chemistry, or radiochemistry. This new endeavor may seem daunting, especially when you consider that you may need to be proficient in areas in which you have not been prepared. This manuscript will illustrate how chemistry, biology, pharmacokinetics, and a host of other disciplines all come together to produce successful new medicines. In order to achieve that goal, we have compiled a collection of fourteen representative categories of drugs that we have carefully chosen from among the best-selling drugs. We have provided an introduction to each drug including a historical perspective, and background to the biology, pharmacology, pharmacokinetics, and drug metabolism followed by a detailed account of the synthesis. The targeted audience goes beyond individuals new to the pharmaceutical industry; many veterans of the industry may well find something new in this text. There are a few points we felt worth reiterating. For example:

a). The advent of new synthetic methodology enables chemists to synthesize drugs in a more convergent and more efficient fashion, a theme seen over and over again in this monograph. Consequently, literature awareness is essential for the chemist in the pharmaceutical industry.

b). Knowing the history of successful drugs and understanding their attributes is very important and the lessons learned can be applied to current programs in drug discovery. A tremendous amount of knowledge has accumulated over the last few decades. Attributes of a successful drug include appropriate potency, selectivity, bioavailability, and physiochemical properties.

c). Serendipity in the drug industry also plays an important role. On the other hand, opportunity favors prepared minds. Many examples can be found in this manuscript. For example, Viagra[®], currently used for erectile dysfunction (ED), was initially developed as a PDE5 inhibitor for hypertension. Likewise, Rogaine[®], currently used topically for hair growth, was first synthesized as a potassium channel opener, also for hypertension. Propecia[®], currently used orally for hair growth, was originally

prepared as a testosterone-5 α -reductase inhibitor for the treatment of benign prostatic hyperplasia (BPH). Therefore, one should be cognizant during the clinical trials; even failure for the initially intended therapeutic indication does not necessarily equate the end of a drug as long as it has been proven to be safe.

d). Another point that medicinal chemists often overlook (sometimes justifiably) is that the synthesis of the drug should be eventually amenable to cost-effective scale-up to make it economically viable. This is where process chemists play an important role. In the subsequent chapters, we have incorporated process synthesis routes when the information was available.

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Brand Names and Their Corresponding USANs

Abilify [®]	aripiprazole
Accutane [®]	isotretinoin
Advair [®]	fluticasone propionate and salmeterol xinafoate
Allegra [®]	fexofenadine
Amerge [®]	naratriptan hydrochloride
Axert [®]	almotriptan malate
Celebrex [®]	celecoxib
Cialis [®]	tadalafil
Cipro [®]	ciprofloxacin
Clarinet [®]	desloratadine
Claritin [®]	loratadine
Crestor [®]	rosuvastatin
Finasteride [®]	finasteride
Flonase [®]	fluticasone propionate
Flovent [®]	fluticasone propionate
Frova [®]	frovatriptan succinate
Geodon [®]	ziprasidone
Gleevec [®]	imatinib mesylate
Imitrex [®]	sumatriptan succinate
Lescol [®]	fluvastatin
Levitra [®]	varidenafil hydrochloride
Lipitor [®]	atorvastatin calcium
Maxalt [®]	rizatriptan benzoate
Mevacor [®]	lovastatin
Nexium [®]	esomeprazole
Paxil [®]	paroxetine hydrochloride
Plavix [®]	clopidogrel
Prilosec [®]	omeprazole
Relpax [®]	eletriptan hydrobromide
Risperdal [®]	risperidone
Pravacol [®]	pravastatin
Prozac [®]	fluoxetine hydrochloride
Rogaine [®]	minoxidil

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Serevent [®]	salmeterol xinafoate
Seroquel [®]	quetiapine fumarate
Singulair [®]	montelukast sodium
Tazorac [®]	tazarotene
Ticlid [®]	ticlopidine
Viagra [®]	sildenafil citrate
Vioxx [®]	rofecoxib
Xenical [®]	orlistat
Zocor [®]	simvastatin
Zoloft [®]	sertraline hydrochloride
Zomig [®]	zolmitriptan
Zyprexa [®]	olanzapine
Zyrtec [®]	cetirizine dihydrochloride
Zyvox [®]	linezolid

Acronyms and Abbreviations

Ac	acetyl
ADP	adenosine diphosphate
ALIQAT	tricaprylmethyl ammonium chloride
cAMP	adenosine cyclic 3',5'-phosphate
ATP	adenosine triphosphate
AUC	area under curve
BER	borohydride exchange resin
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMI	body mass index
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
BPH	benign prostatic hyperplasia
BSTFA	bis(trimethylsilyl)-tri fluoroacetamide
<i>t</i> -Bu	<i>tert</i> -butyl
CL	total clearance
CL _R	renal clearance
CML	chronic myeloid leukemia
CNS	central nervous system
COX-2	cyclooxygenase II
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
CSF	cerebral synovial fluid
5-CT	5-carbamoyltryptamine
CYP	cytochrome
DABCO	1,4-diazabicyclo[2.2.2]octane
DALYS	Disability Adjusted Life Years
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
<i>o</i> -DCB	<i>o</i> -dichlorobenzene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DHT	5 α -dihydrotestosterone
DNA	deoxy-nucleic acid
ECG	ecocardiograms
ED	erectile dysfunction
EGF	epidermal growth factor
EPS	extrapyramidal side-effects
FDA	Food and Drug Administration
Fen-Phen	fenfluramine and phentermine
GI	gastrointestinal
GISA	glycopeptide-intermediate <i>S. aureus</i>

CGMP	cyclic guanosine monophosphate
GPCRs	G-protein-coupled receptors
HMG-CoA	hydroxymethylglutaryl coenzyme A
HMGR	HMG-CoA reductase
HMPA	hexamethylphosphoric triamide
HPL	human pancreatic lipase
HPLC	high-performance liquid chromatography
5-HT	5-hydroxytryptamine (serotonin)
KCO	potassium channel opener
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
LTs	leukotrienes
MAO	monoamine oxidase
MDD	major depressive disorder
MICs	minimal inhibition concentrations
MMPP	magnesium monoperoxyphthalate hexahydrate
MOA	mechanism of action
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
PCC	pyridinium chlorochromate
PDE5	phosphodiesterase-5
PDGFR	platelet-derived growth factor receptor, a kinase
PG	prostaglandin
PK	pharmacokinetics
PKC	protein kinase C
PLE	pig liver esterase
PPH	primary pulmonary hypertension
PPI	proton pump inhibitor
RA	rheumatoid arthritis
Ra-Ni	Raney-Nickel
RCM	ring-closing metathesis
RNA	ribonucleic acid
RT	room temperature
SDAs	serotonin-dopamine antagonists
S _N Ar	nucleophilic substitution on an aromatic ring
S _N 1	unimolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
SNRI	serotonin and noradrenaline reuptake inhibition
SPOS	solid phase organic synthesis
SSRI's	selective serotonin reuptake inhibitors
T	testosterone
Tbf	tetrabenzo[<i>a,c,g,i</i>]fluorene

TBS	<i>tert</i> -butyldimethylsilyl
TCAs	tricyclic antidepressants
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TKI	tyrosine kinase inhibitor
TMEDA.....	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMG.....	tetramethylguanidine
Tol	toluene or tolyl
Ts.....	tosylate
USAN.....	United States Adopted Names
UV	ultraviolet
VRE.....	vancomycin-resistant enterococci
V _{ss}	steady-state volume of distribution